Torino, 5 aprile 2022

CLL CASE REPORT

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CLL Case report – Clinical history (2022)

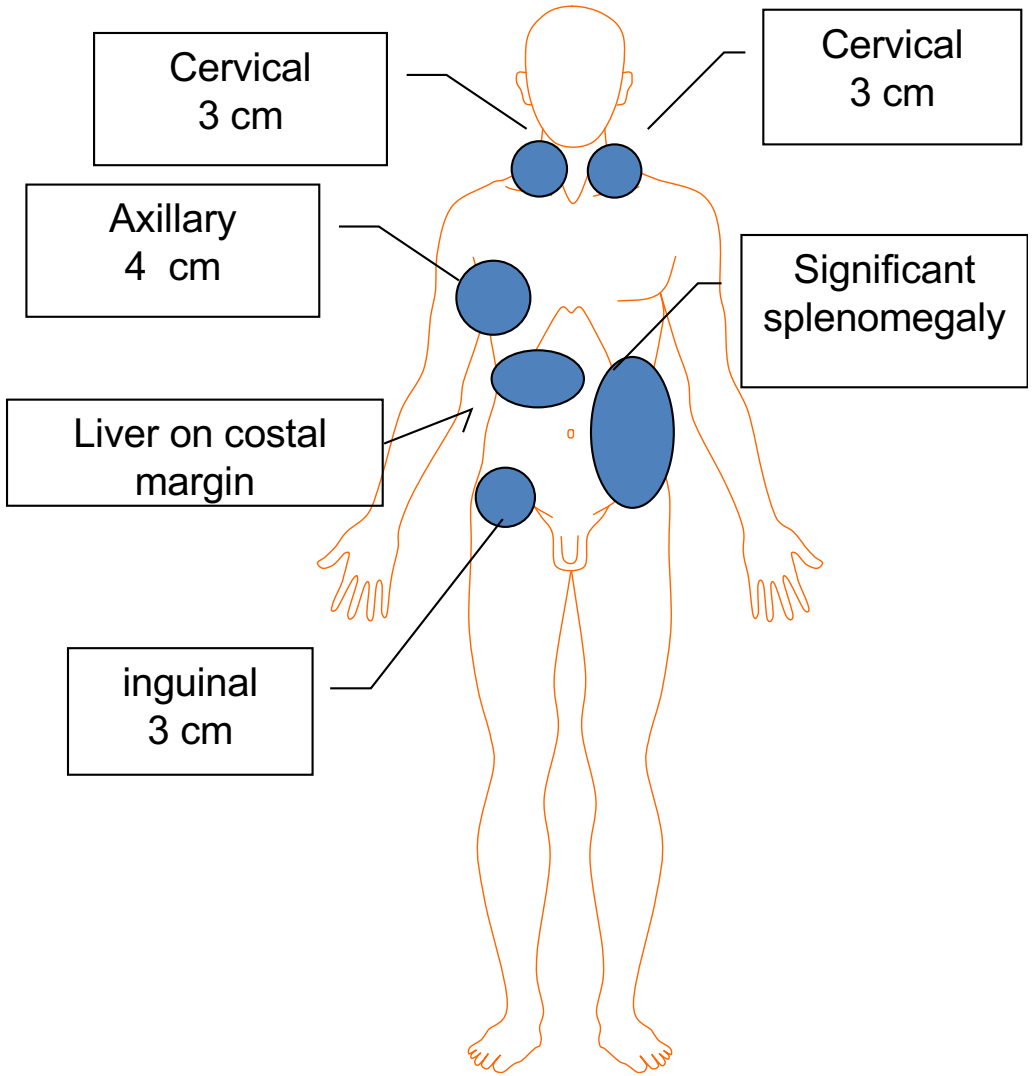
- ✓ Male, 78-years-old at diagnosis, ECOG-PS 0
- ✓ Hypertension, dyslipidaemia, ischemic cardiopathy, previous episode of atrial fibrillation in DOACs
- ✓ He was referred to our institution for a thrombocytopenia, adenopathies and splenomegaly

Laboratory tests and physical examination (2022)

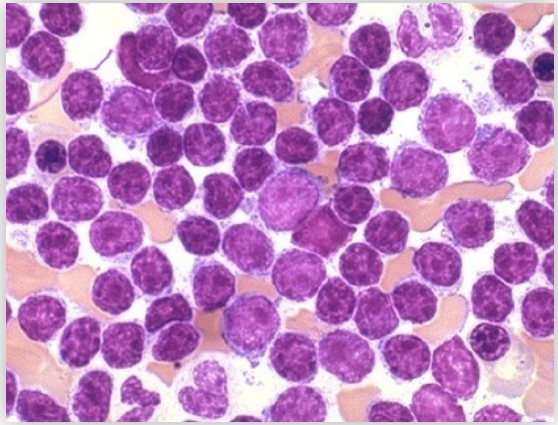
Laboratory tests

Parameters	Values	Reference values
WBC	**89 x10⁹/l**	4.0-10.0 x10⁹/l
ALC	**85 x10⁹/l**	1.0-4.5 x10⁹/l
Hb	**10.4 g/l**	135-175 g/l
PLT	**74 x10⁹/l**	150-450 x10⁹/l
Total bilirubin	10 mmol/l	3-22 mmol/l
LDH	432 IU/l	208-450 IU/l
IgG	**3.6 g/l**	6-16 g/l
IgA	**0.8 g/l**	0.9-4.5 g/l
IgM	**0.3 g/l**	0.5-2 g/l
B2M	**3.0 mg/l**	0-2.3 mg/l
HCV serology	negative	
HIV serology	negative	
HBsAg	negative	
HBcAb/HBsAb	Negative	
DAT/IAT	negative	

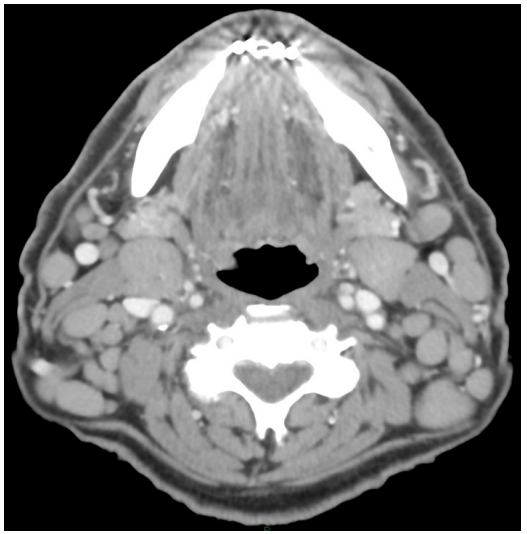
Physical examination
Lymphadenopathy and splenomegaly

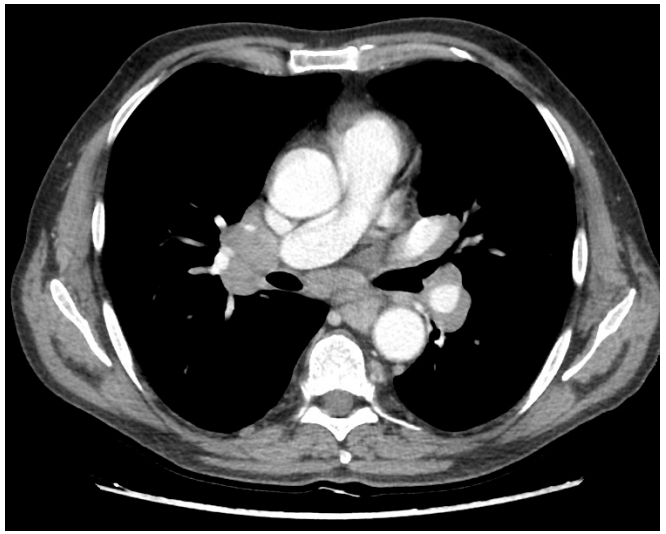


CLL Case report – Staging (2022)

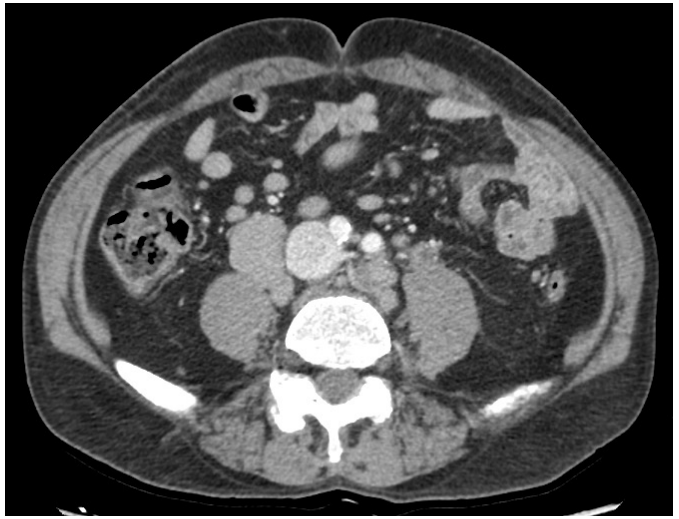


Bone marrow biopsy:
massive infiltration by small B lymphocytes
CD5+CD23+(90%)



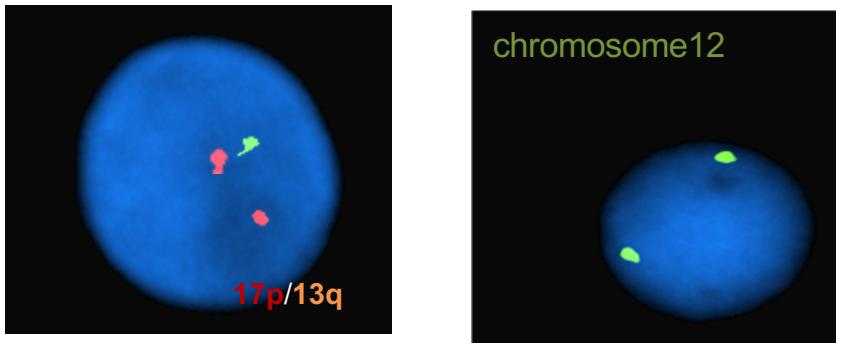


CT:
lymphadenopathy – max 4-5 cm nodes at multiple sites, splenomegaly 20 cm

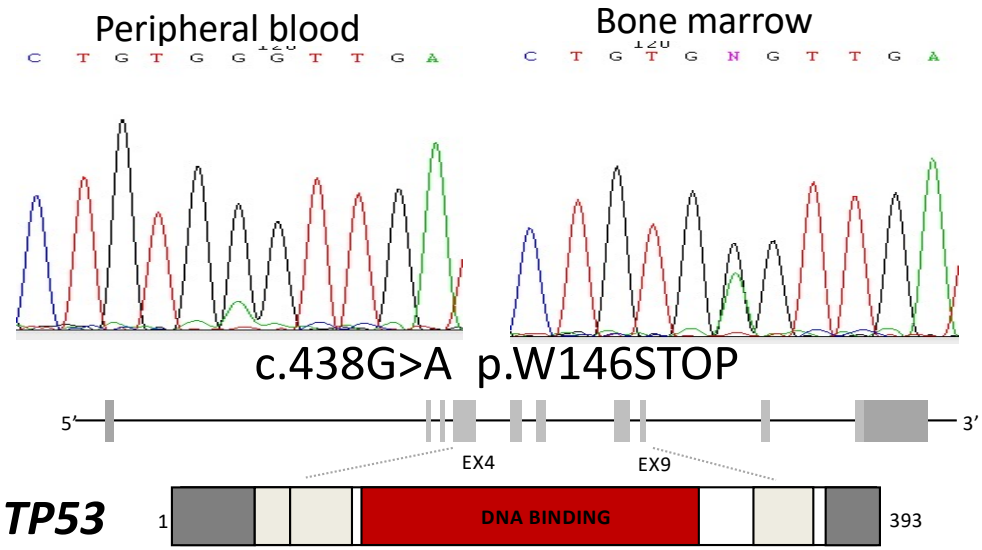


Clinical case: Biological parameters

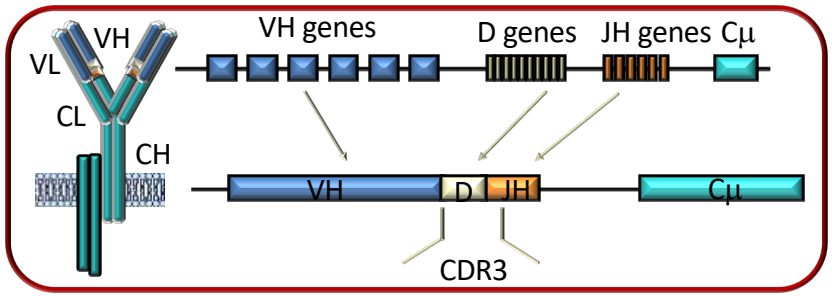
- ✓ Fluorescence *in situ* hybridisation (FISH): 17p deletion



- ✓ *TP53* mutational status: MUTATED



- ✓ UnMutated *IGHV* 4-34*01

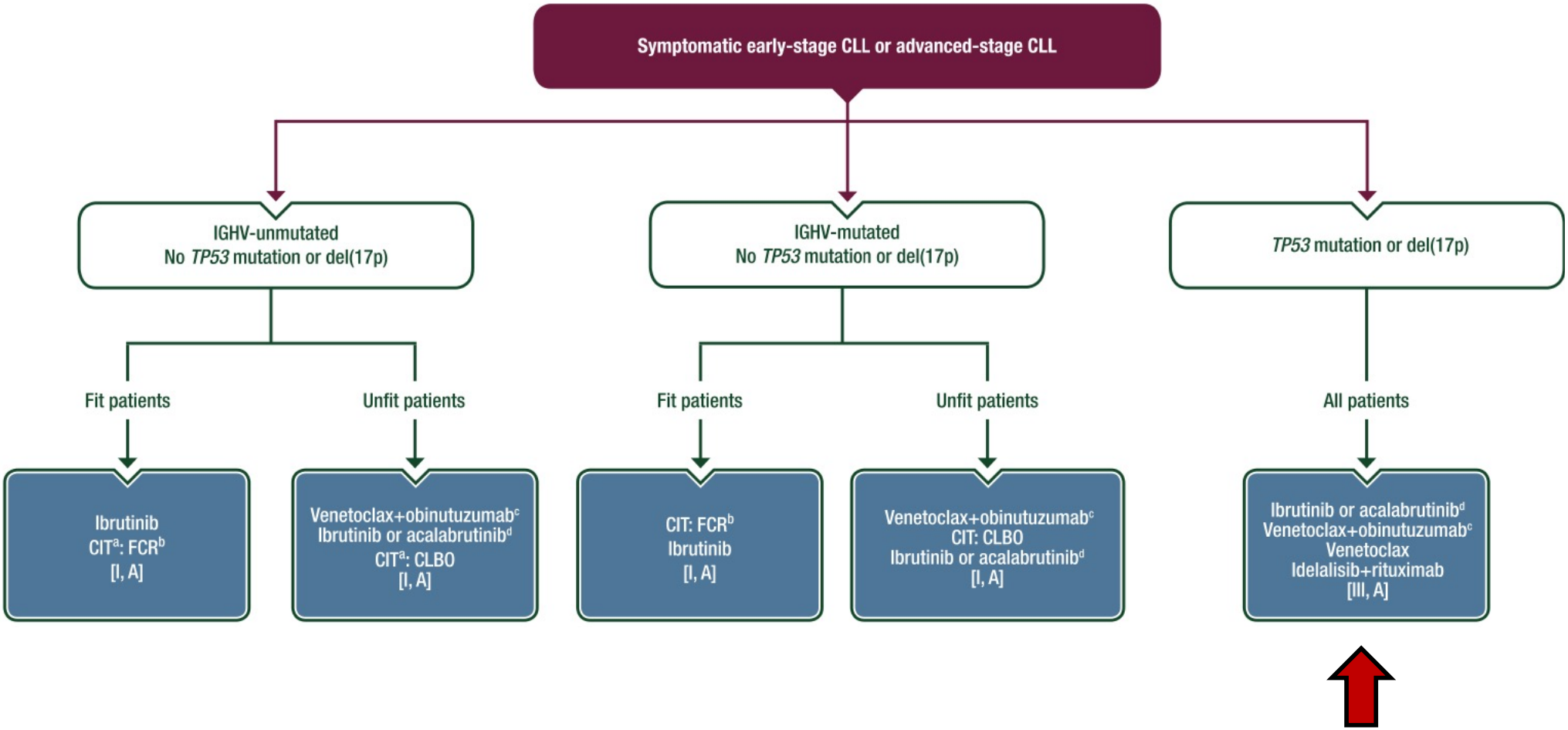


CLL Case report – Clinical history (2022)

- ✓ Elderly CLL patient, Rai IV/Binet C, symptomatic for splenomegaly, anemia and thrombocytopenia, *TP53* disrupted
- ✓ ECOG-PS 0
- ✓ CIRS score 6 (cardiological disease, previous AF, currently in DOACs)

NEED FOR TREATMENT

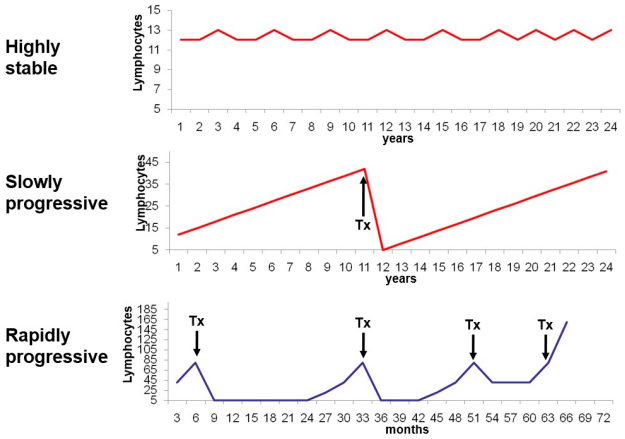
Treatment algorithm



Eichhorst *et al., Ann Oncol*. 2021

CLL pts management depends on different variables

Biological and clinical features of disease



Patient features

→Age
→Comorbidities
→ECOG-PS
→Bone marrow reserve
→QoL

Treatment adopted

→ CHT vs small molecules
→Fixed vs untill PD treatment

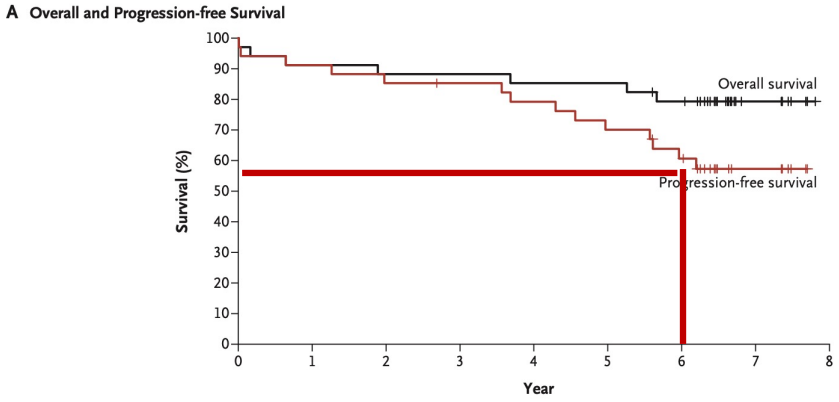
Complications

- Infections (COVID era)
- Autoimmunity
- Secondary neoplasia

TREATMENT DECISION, SUPPORTIVE CARE AND LONG TERM MANAGEMENT

BTKi are highly active in *TP53* disrupted patients

IBRUTINIB
Phase 2 trial

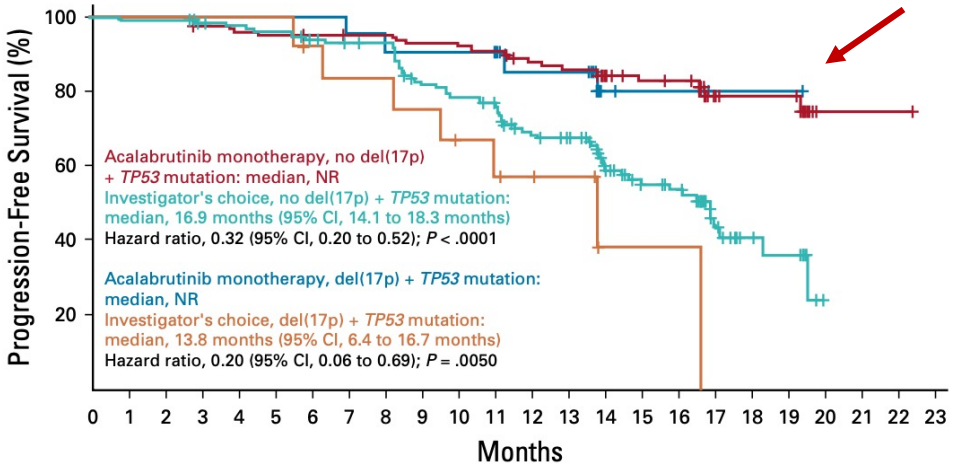


B Summary of Survival

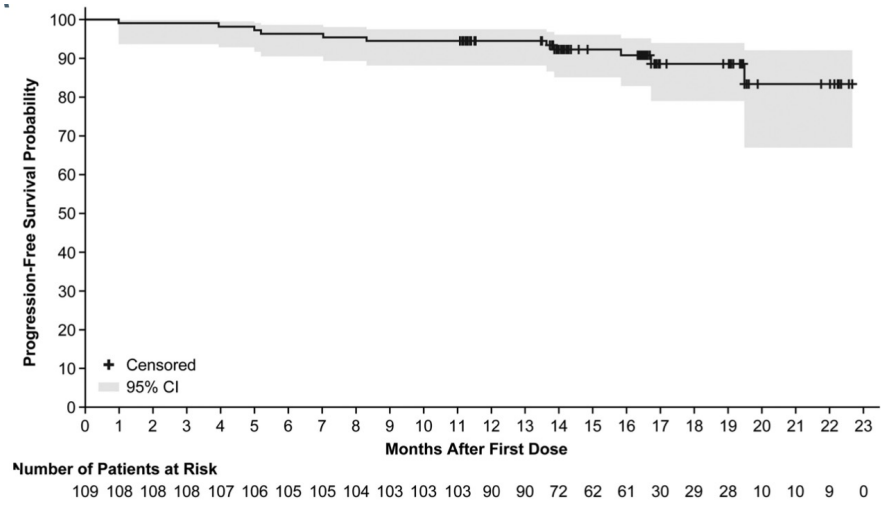
	2 Yr	3 Yr	4 Yr	5 Yr	6 Yr
			% (95% CI)		
Overall Survival	88 (78–100)	88 (78–100)	85 (74–98)	85 (74–98)	79 (67–94)
Progression-free Survival	85 (74–98)	85 (74–98)	79 (67–94)	70 (56–88)	61 (46–80)

In ibrutinib arm CLL with TP53 anomalies have 6y PFS: 61%

ACALABRUTINIB
ASCEND

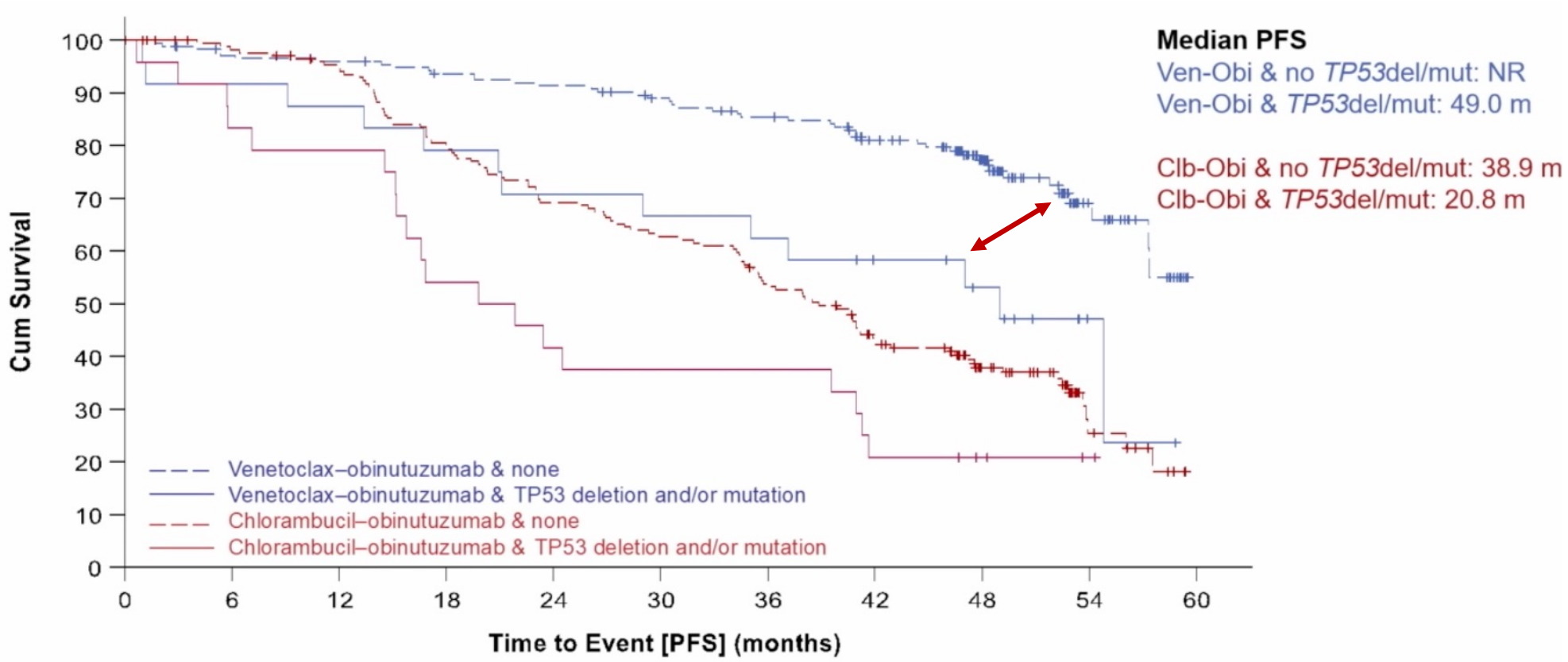


ZANUBRUTINIB
ARM-C SEQUOIA TRIAL



Ahn *et al*., *NEJM*. 2020; Ghia *et al., JCO*. 2020; Tam *et al., Haematologica*. 2021.

Clinical impact of *TP53* in the CLL14 trial (Obinutuzumab-venetoclax)



- ✓ **Ven-Obi improves, but not abolishes, the negative prognostic impact of *TP53* disruption (mPFS 49 months)**
- ✓ **Lower number pts (8.5% 17pDel and TP53 Mut 11% CLL-14 trial population) and shorter FU compared to ibrutinib**

Al-Sawaf *et al.*, EHA 2021 S146

PROs and CONs of BTKi and BCL2i in front line setting

	BTKi	BCL2i
PROs	• Easy to initiate and low risk of TLS • Effective in all prognostic group	• Limited duration therapy • Low toxicity and very tolerable profile once ramped up • Limited duration may reduce risk of resistance mutations?
CONs	• Continuous therapy • Cardiovascular side-effects	• Logistic of TLS monitoring • *TP53* aberrant and IGHV unmutated lower PFS

Ibrutinib is probably more effective than BCL2i in CLL pts harboring TP53 disruptions, BUT it has significant cardiovascular side-effects

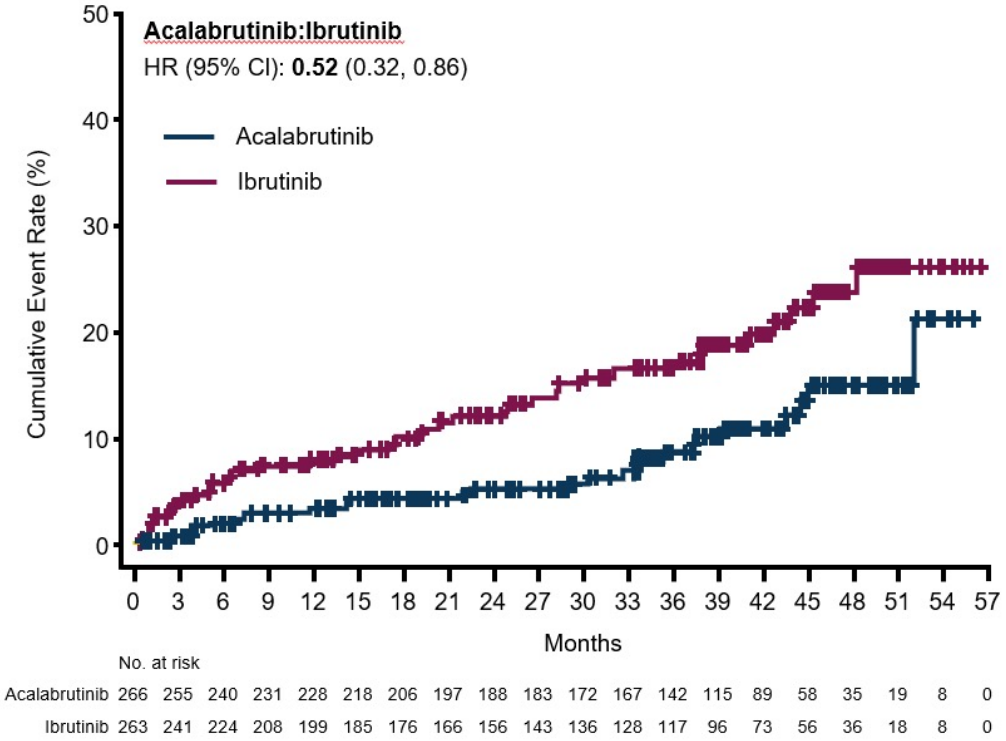
2nd generation BTKis show a lower incidence of side-effect, especially cardiovascular toxicity

Incidence of F is lower with acalabrutinib than ibrutinib in ELEVATE RR trial (Del17p De11q R/R CLL)

	Any grade	
	Acalabrutinib (n=266)	Ibrutinib (n=263)
Atrial fibrillation/flutter	**25 (9.4)*,[a]**	**42 (16.0)[a]**
Events/100 person-months	0.366	0.721
Time to onset, months, median (range)	**28.8** (0.4–52.0)	**16.0** (0.5–48.3)
Leading to treatment discontinuation[b]	0	7 (16.7)
Afib/flutter incidence among patients without prior history of afib/flutter	15/243 (**6.2**)	37/249 (**14.9**)

Incidence of Atrial fibrillation/flutter of any grade were **significantly lower with acalabrutinib** vs ibrutinib (9.4% vs 16%; **P=0.02**)

Cumulative incidence of atrial fibrillation/flutter is lower with acalabrutinib (HR 0.52)



Byrd JC et al. *J. Clin. Oncol.* 2021

Incidence of AF is lower with zanubrutinib than ibrutinib in ALPINE phase 3 trial (R/R CLL)

- ✓ Median FU: 15 months
- ✓ Discontinuation 11% zanubrutinib vs 24% ibrutinib
- ✓ Discontinuation for AEs: 7% zanubrutinib vs 13 % ibrutinib

Safety Analysis Population	Zanubrutinib (n=204), n (%)		Ibrutinib (n=207), n (%)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Cardiac disorders[a]	28 (13.7)	5 (2.5)	52 (25.1)	14 (6.8)
Atrial fibrillation and flutter (key 2º endpoint)	**5 (2.5)**	**2 (1.0)**	**21 (10.1)**	**4 (1.9)**
Hemorrhage	73 (35.8)	6 (2.9)	75 (36.2)	6 (2.9)
Major hemorrhage[b]	6 (2.9)	6 (2.9)	8 (3.9)	6 (2.9)
Hypertension	34 (16.7)	22 (10.8)	34 (16.4)	22 (10.6)
Infections	122 (59.8)	26 (12.7)	131 (63.3)	37 (17.9)
Neutropenia[c]	58 (28.4)	38 (18.6)	45 (21.7)	31 (15.0)
Thrombocytopenia[c]	19 (9.3)	7 (3.4)	26 (12.6)	7 (3.4)
Secondary primary malignancies	17 (8.3)	10 (4.9)	13 (6.3)	4 (1.9)
Skin cancers	7 (3.4)	3 (1.5)	10 (4.8)	2 (1.0)

AEs of Special Interest

Lower rate of atrial fibrillation and flutter with zanubrutinib (2.5% vs 10%)

Hillmen P et al, EHA 2021

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NEED FOR TREATMENT

TREATMENT

FEB 2022: Start zanubrutinib compassionate use

FOLLOW UP

APR 2022: no relevant toxicities (>2), significant reduction of adenopathies and splenomegaly

Attention is the rarest and purest form of generosity
Simone Weil

THANKS FOR YOUR ATTENTION